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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/287,632	04/07/1999	PETER MICHAEL WATERHOUSE	021565-060	6526

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
11/01/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/287,632	WATERHOUSE ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12,22,26,40,42-44,46,50,53,54,56,58 and 63-108* is/are pending in the application.

4a) Of the above claim(s) *1-10, 12, 40, 43, 44, 46, 50, 70-84, 98, 99, 104, 105* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,26,42,53,54,56,58,63-69,85-97,100-103 and 106-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communications filed 8-8-07.

Claims 1-10, 12, 22, 26, 40, 42-44, 46, 50, 53, 54, 56, 58, 63-108 are pending in the instant application. Claims 1-10, 12, 40, 43, 44, 46, 50, 70-84, 98, 99, 104, 105 are withdrawn as being drawn to a non-elected invention, and claims 22, 26, 42, 53, 54, 56, 58, 63-69, 85-97, 100-103 and 106-108 have been examined on their merits as set forth below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The declarations under 37 CFR 1.132 filed 8-8-07 are insufficient to overcome the rejection of claims 22, 26, 42, 53, 54, 56, 58, 63-69, 85-97, 100-103 and 106-108 based upon 35 U.S.C. 112, first paragraph as set forth in the last Office action and for the reasons set forth below.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 22, 26, 42, 53, 54, 56, 58, 63-69, 85-97, 100-103, 106-108 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description

requirement for the reasons of record set forth in the Office action mailed 2-8-07 and for the reasons set forth below.

Applicant's arguments and declarations filed 8-8-07 have been fully considered but they are not persuasive. The claims are drawn to plants, eukaryotic cells, and chimeric DNA comprising an operable promoter, transcription termination and polyadenylation region, and further comprising a DNA region encoding a region capable of forming an artificial hairpin RNA structure with a double stranded RNA stem by base pairing between regions with a sense and an antisense nucleotide sequence, which sense nucleotide sequence includes at least 10 consecutive nucleotides having 100% sequence identity with at least 10 consecutive nucleotides of a nucleic acid of interest, and which antisense sequence includes at least 10 consecutive nucleotides having 100% sequence identity with said at least 10 consecutive nucleotides of the sense sequence, and which chimeric DNA further comprises any intronic sequence.

Applicant argues that adequate written description has been provided for the claimed invention, whereby the location of an intron anywhere in the construct is not critical for enhancing the efficiency of target gene silencing. Applicant provides several post-filing publications in support of the general applicability of the use of intronic sequences for enhancing efficiency of target gene silencing using dsRNA. Applicant additionally argues that the explanations provided both in the references and the declarations filed 8-8-07 implicate the excision or splicing process.

Contrary to Applicant's assertions, the limitations of excision or splicing signals as part of the intronic sequences are not recited in the claims. Furthermore, the reference provided by Applicant provides a much broader definition of intronic sequences: "Introns range in size from about 80 to 10,000 nucleotides or more. They differ dramatically from exons in that their exact nucleotide sequences seem to be unimportant... The only highly conserved sequences in introns are those required for intron removal." (See Alberts et al., Molecular Biology of the Cell (2nd. Ed.) at p. 533). The vast variability of intron sequences has been described elsewhere in the art: "What is an intron in one cell's nucleus may be an exon in another cell's nucleus. Alternative RNA processing has been found to control the alternative forms of expression of over 100 proteins. The deletion of certain potential exons in some cells but not in others enables one gene to create a family of closely related proteins..." (Gilbert, S.F., Developmental Biology, (Sinauer Assoc., Inc.: Mass., 1997) at p. 466).

The specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of the broad genus comprising DNA constructs whereby any intronic sequence is inserted anywhere in the chimeric DNA, and whereby the DNA construct provides for the function claimed, of generating a gene silencing construct that reduces phenotypic expression of any nucleic acid of interest in any plant and in any eukaryotic cell. The specification teaches fully complementary pair constructs for reducing the phenotypic expression of a transgenic Gus gene (of approximately 1580 base pairs), and complementary pair constructs for

reducing the phenotypic expression of the Δ12 desaturase target gene in *Arabidopsis* (of approximately 620 base pairs) which complementary pair constructs additionally comprise the pyruvate orthophosphate dikinase 2 intron 2 from *Flaveria trinervia* (SEQ ID NO. 7) in forward or reverse orientation. The scope of the claims, however, includes a vast myriad of structural variants, and the genus is highly variant because a significant number of structural differences between members of this very broad genus are permitted. For these reasons, the limitations that Applicant asserts are implicated (e.g. by the post-filing publications and declarations filed on 8-8-07) do not exist in the claims and are not reasonably supported by the broadest interpretation of the claim language, nor by a reasonable definition of the intronic sequences by one of skill in the art.

New Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 22, 26, 42, 53, 54, 56, 58, 63-69, 85-97, 100-103 and 106-108 are rejected under 35 U.S.C. 102(b) as being anticipated by Flavell.

Flavell (Proc. Natl. Acad. Sci., Vol. 91, pages 3490-3496, 1994) teaches plants, eukaryotic cells, and chimeric DNA comprising an operable promoter, transcription termination and polyadenylation region, and further comprising a DNA region encoding a region capable of forming an artificial hairpin RNA structure with a double stranded RNA stem by base pairing between regions with a sense and an antisense nucleotide sequence, which sense nucleotide sequence includes at least 10 consecutive nucleotides having 100% sequence identity with at least 10 consecutive nucleotides of a nucleic acid of interest, and which antisense sequence includes at least 10 consecutive nucleotides having 100% sequence identity with said at least 10 consecutive nucleotides of the sense sequence, and which chimeric DNA further comprises any intronic sequence (see esp. the abstract and text on pp. 3490-3491).

Claims 22, 26, 42, 53, 54, 56, 58, 63-69, 85-97, 100-103 and 106-108 are rejected under 35 U.S.C. 102(b) as being anticipated by Metzlaff et al.

Metzlaff et al (Cell, Vol. 88, pages 845-854, 1997) teach plants, eukaryotic cells, and chimeric DNA comprising an operable promoter, transcription termination and polyadenylation region, and further comprising a DNA region encoding a region capable of forming an artificial hairpin RNA structure with a double stranded RNA stem by base pairing between regions with a sense and an antisense nucleotide sequence, which sense nucleotide sequence includes at least 10 consecutive nucleotides having 100% sequence identity with at least 10 consecutive nucleotides of a nucleic acid of interest, and which antisense sequence includes at least 10 consecutive nucleotides having 100% sequence identity with said at least 10 consecutive nucleotides of the sense sequence, and which chimeric DNA further comprises any intronic sequence (see esp. fig. 1 and 2 on p. 846; Table 1 and text on p. 849; text on p. 850; fig. 7 on p. 852).

Claims 22, 26, 42, 53, 54, 56, 58, 63-69, 85-97, 100-103 and 106-108 are rejected under 35 U.S.C. 102(b) as being anticipated by Stam et al.

Stam et al (Annals of Botany, Vol. 79, pages 3-12, 1997) teach plants, eukaryotic cells, and chimeric DNA comprising an operable promoter, transcription termination and polyadenylation region, and further comprising a DNA region encoding a region capable of forming an artificial hairpin RNA

structure with a double stranded RNA stem by base pairing between regions with a sense and an antisense nucleotide sequence, which sense nucleotide sequence includes at least 10 consecutive nucleotides having 100% sequence identity with at least 10 consecutive nucleotides of a nucleic acid of interest, and which antisense sequence includes at least 10 consecutive nucleotides having 100% sequence identity with said at least 10 consecutive nucleotides of the sense sequence, and which chimeric DNA further comprises any intronic sequence (see esp. bridging paragraph on pp. 3-4; fig. 1 on p. 4; fig. 3 on p. 9).

Claims 22, 26, 42, 53, 54, 56, 58, 63-69, 85-97, 100-103 and 106-108 are rejected under 35 U.S.C. 102(e) as being anticipated by Fire et al.

Fire et al (USPN 6,506,559) teach plants, eukaryotic cells, and chimeric DNA comprising an operable promoter, transcription termination and polyadenylation region, and further comprising a DNA region encoding a region capable of forming an artificial hairpin RNA structure with a double stranded RNA stem by base pairing between regions with a sense and an antisense nucleotide sequence, which sense nucleotide sequence includes at least 10 consecutive nucleotides having 100% sequence identity with at least 10 consecutive nucleotides of a nucleic acid of interest, and which antisense sequence includes at least 10 consecutive nucleotides having 100% sequence identity with said at least 10 consecutive nucleotides of the sense

sequence, and which chimeric DNA further comprises any intronic sequence (see esp. the abstract; col. 4, lines 41-61; col. 6, line 32-col. 9, line 48; col. 12, lines 46-col. 13, line 8; claims 1-12 and 21).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22, 26, 42, 53, 54, 56, 58, 63-69, 85-97, 100-103 and 106-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al in view of Brown et al, Lusky et al and Schiedner et al, the combination in view of Baracchini et al.

The claims are drawn to plants, eukaryotic cells, and chimeric DNA comprising an operable promoter, transcription termination and

polyadenylation region, and further comprising a DNA region encoding a region capable of forming an artificial hairpin RNA structure with a double stranded RNA stem by base pairing between regions with a sense and an antisense nucleotide sequence, which sense nucleotide sequence includes at least 10 consecutive nucleotides having 100% sequence identity with at least 10 consecutive nucleotides of a nucleic acid of interest, and which antisense sequence includes at least 10 consecutive nucleotides having 100% sequence identity with said at least 10 consecutive nucleotides of the sense sequence, and which chimeric DNA further comprises any intronic sequence.

Fire et al (USPN 6,506,559) teach plant cells, plants and their seeds comprising a nucleic acid comprising a first and second DNA sequence which expresses in the plant cell a chimeric DNA comprising a promoter, operatively linked to a DNA region which, when transcribed, yields and RNA molecule capable of forming a hairpin comprising two annealing RNA sequences which comprise a sense sequence sharing homology with consecutive nucleotides of a target nucleic acid of interest in the plant, and which further comprises a second, annealing RNA sequence comprising antisense sharing homology with the consecutive nucleotides of the sense strand that targets the nucleic acid of interest, and which chimeric DNA further comprises an intron sequence, and which chimeric DNA further comprises operably linked transcription termination and polyadenylation sequences (See the abstract, col. 3-4, col. 5, line 47-col. 6, line 54, col. 7, line 42-col. 9, line 25, col. 11, line 37-col. 12, line 8, col. 17, line 20-24, col. 21, line

36-col. 22, line 4; col. 4, lines 41-61; col. 6, line 32-col. 9, line 48; col. 12, lines 46-col. 13, line 8; claims 1-12 and 21).

Fire et al (USPN 6,506,559) do not teach the targeting region of the chimeric construct to span between 10 and 50 consecutive nucleobases.

Brown et al (USPN 5,859,347) teach plant cells transformed with chimeric nucleic acid expression constructs expressing desired DNA sequences, and which expression constructs comprise expression elements including operably linked promoters and further comprising heterologous introns, which introns enhance stability and expression of the nucleic acid sequences in an expression construct (see col. 8, line 53-col. 9, line 17, examples 1-7 in cols. 10-18 and figures 8-27).

Lusky et al (USPN 6,350,575) teach expression constructs comprising antisense RNA and further comprising an intron as well as other expression elements including translation termination and polyadenylation signals (col. 6, line 15-col. 7, line 14).

Schiedner et al (Nature: Genetics, Vol. 18, pages 180-183, 1998) teach expression vectors comprising intronic sequences for enhancing vector stability (see esp. left col., p. 180).

Baracchini et al (USPN 5,801,154) teach the motivation and ability to target a gene of interest with a complementary sequence comprising at least 10 nucleobases (see e.g. claims 1, 12, 26, and 32).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to alter the expression of a target gene of known sequence, which gene is either endogenous or heterologous to a plant cell, which target gene is either

stably integrated or extrachromosomal, comprising the introduction of nucleic acids comprising sense and complementary antisense sequences of the target gene, which are operably linked to a constitutive or heterologous promoter, and which are optionally expressed on separate or the same expression construct, and hybridize after their expression to the complementary sequences of each other to form a double stranded molecule, whereby a duplex is formed between the expressed sense and antisense fragments, because the efficiency of such methods of gene silencing have been previously taught Fire et al. One of ordinary skill in the art would have expected the expressed double stranded RNA to target and inhibit the expression of corresponding target sequences of a target gene of known sequence, as taught previously by Fire et al. One of ordinary skill in the art would have been motivated to include intronic sequences within the expression constructs for gene expression in plants because the use of intronic sequences for enhancing vector stability and hence enhance expression of a desired gene in cells had been taught previously by Brown et al and Schiedner et al. And Lusky et al and Fire also teach the incorporation of intronic sequences in expression constructs and it was well known in the art that the inclusion of introns enhances the expression of RNA in plants. One of ordinary skill in the art would have optionally placed the intronic sequences between the sense and antisense sequences in the chimeric construct originally taught by Fire et al because this is a design choice and additional, non-complementary sequences (e.g. intronic sequences) are included in the sense antisense constructs in order to allow for hairpin turns between complementary sequences. One of ordinary skill in the art would have expected that

the intronic sequences, inserted at different places in the expression construct, would enhance expression of the chimeric constructs in plants and it would take routine experimentation to determine where in the construct the intron sequences would be inserted, as long and complementarity between the sense and antisense sequences was maintained for subsequent target gene inhibition. One of ordinary skill in the art would have been motivated to include between 10 – 50 nucleobases for the double stranded gene silencing construct because Fire et al teaches these constructs to be in that range (e.g. 25 nucleobases) and it would take routine experimentation to vary and broaden the range of sequences of the gene silencing constructs originally taught by Fire et al. Likewise, one of ordinary skill in the art would have expected that the range of 10-50 nucleobases, and sharing 100% homology would be effective in gene silencing, because Fire et al taught that at least 10% of the target sequences could be changed and gene silencing still occur, and successful gene targeting has been routinely provided using antisense with a minimum length of 10 nucleobases (see also Baracchini et al). It would therefore take routine experimentation to alter the length of the target sequence as well as the homology required for successful gene silencing in plant cells. One would have been motivated to express downstream and operatively linked sequences in DNA expression vectors to subsequently duplex RNA in a cell to target and inhibit target gene expression.

One of ordinary skill in the art would have been motivated to inhibit the expression of target genes by these expressed RNAi molecules, as described previously by Fire et al, for altering cellular phenotypes in order to study gene function,

or to study the role of various target genes by comparing cellular processes in the absence or presence of these target genes expression, or to inhibit a deleterious pathogenic gene of an invading organism in a plant cell by inhibiting pathogenic target gene expression using this technique of gene silencing. One of ordinary skill in the art would have expected that the inclusion of intronic sequences would enhance expression construct stability because the inclusion of intronic sequences in expression constructs was routine in the art, as evidence by the inclusion of intronic sequences in commercial and other published expression constructs, at the time the invention was made. One of ordinary skill in the art would have expected that the transformation of expression cassettes for target gene silencing in appropriate plant cells, whereby the concerted expression of both the sense and antisense fragments in appropriate target cells using appropriate promoters is obtained, leads to the formation of double stranded fragments directed to the target gene sequences in the transformed cells, and consequently interferes with the expression of the target gene, thereby producing inhibition of target gene expression, allowing a comparison of cellular phenotypes in the presence and absence of target gene inhibition, as taught previously by Fire et al.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices

published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
10-24-07

JANE ZARA, PH.D.
PRIMARY EXAMINER